

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Hypertension in the South African Public Healthcare System: A Cost-of-Illness and Burden of Disease Study
AUTHORS	Kohli-Lynch, Ciaran; Erzse, Agnes; Rayner, B; Hofman, Karen

VERSION 1 – REVIEW

REVIEWER	Eduardo Augusto Fernandes Nilson Ministry of Health of Brazil, Department of Health Promotion
REVIEW RETURNED	31-Aug-2021

GENERAL COMMENTS	<p>Overall, the manuscript "Hypertension in the South African Public Healthcare System: Health and Economic Burden of Disease" investigates an interesting research question. In particular, the study estimates the direct and societal costs of hypertension to the public health system in South Africa. Overall, the manuscript is clearly written and accessible to non-specialists and makes a welcomed contribution to the literature in this area with clear implications for public policy.</p> <p>Introduction</p> <p>- More summary information on the burden of hypertension in South Africa would help readers to better understand the context in which the study takes place. For example, the introduction would benefit from having more information on the health burden of hypertension and its historical trends, such as the annual deaths.</p> <p>Methods</p> <p>Generally clear.</p> <p>There seemed to be no consideration of the likely time lags between the intervention, and the change in disease incidence.</p> <p>In the societal costs, it could be detailed that DALYs encompass premature deaths and years lived with disability in the productivity losses.</p> <p>Also regarding societal costs (productivity losses), the retirement age for men and women in South Africa is 60 years, so why were the estimates extended to 65 years of age?</p> <p>Sensitivity analysis is clear and explored well the influence of variables in the modeled results.</p> <p>Results:</p> <p>It would be helpful to detail the results based on sex differences. Table 4 should include 95% CI.</p> <p>Discussion</p> <p>The estimates are associated to the economic burden of hypertension to the public health system, so the overall costs of disease are even higher (considering the population covered by</p>
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	private health care). The estimates rely on the GBD estimates, therefore the general limitations related to the GBD data should be added to the discussion.
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REVIEWER	Nicole Fraser-Hurt The World Bank Group
REVIEW RETURNED	13-Sep-2021

GENERAL COMMENTS	<p>This is a very important and well executed analysis. It employs a thorough approach to estimate health, cost and economic burdens in the uninsured South African population. Congratulations to the researchers.</p> <p>My comments and suggestions are all minor.</p> <p>P6, line 52: "Individuals who met two criteria (e.g., SBP 150 mm Hg and DBP 105 mm Hg) were included in the more severe hypertension category." You present the grade 3/severe category and then give this example of a case with grades 1b/2 BP data, calling it 'more severe'. This is confusing.</p> <p>P9, line 54: If hypertension was skewed toward poorer population groups then the 1 GDP/capita assumption may be an overestimate of the cost of lost productivity due to very low incomes? Given the estimations have shown sensitivity to this assumption, you could add a caveat that you did not take into account the distribution of hypertension by income levels in the lost productivity estimates?</p> <p>P11, line 27: You mention that hypertension prevalence had, among other factors, a large impact on total cost estimates, and that substantial reductions in direct medical and societal costs could be achieved if the prevalence of hypertension were to be reduced. Doesn't the poor treatment success among those diagnosed and on treatment also have a major effect on costs? Less than half of those diagnosed are controlling their BP (est. 46%), which compares well to many other countries but nevertheless drives the total costs.</p> <p>Page 13, line 6: You conclude that "Research is required to establish priority cost-effective strategies for lowering rates of hypertension and preventing complications". Isn't much of this research available, and now needs to be translated into quality service delivery, where guidelines are implemented and care is convenient and accessible? You could emphasize in the conclusions that improvements in the management of the already diagnosed hypertension cases is urgently needed to avert costs of illness to the health sector and society.</p> <p>Table 1: Hypertension-related complications – Does this include costs of rehabilitation? Correct the cost for physician visit (typo) - 17.11.00</p> <p>Table 4: CKD complications – the costs in the two currencies don't match (ZAR 19 / USD 94)</p> <p>Supplement: II. Treatment to Manage Hypertension – You clearly cost the implementation of this multi-step treatment escalation guidance. It might be useful to mention it in the text that you are guideline-costing and not actual treatment as implemented in practice.</p> <p>Tables 4, 5 and 7: Please indicate which costs are annual</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Dr. Eduardo Augusto Fernandes Nilson, Ministry of Health of Brazil, University of Sao Paulo

Comments to the Author: Overall, the manuscript "Hypertension in the South African Public Healthcare System: Health and Economic Burden of Disease" investigates an interesting research question. In particular, the study estimates the direct and societal costs of hypertension to the public health system in South Africa. Overall, the manuscript is clearly written and accessible to non-specialists and makes a welcomed contribution to the literature in this area with clear implications for public policy.

Response – Thank you for taking time to review our paper and thank you for the suggested adjustments to our modelling and manuscript.

Introduction: More summary information on the burden of hypertension in South Africa would help readers to better understand the context in which the study takes place. For example, the introduction benefit from having more information on the health burden of hypertension and its historical trends, such as the annual deaths.

Response – Thank you for this suggestion. We have included the following text in the *Background* section of the manuscript (references are listed at the end of this document):

"High blood pressure (BP), or hypertension, caused an estimated 10.7 million deaths worldwide in 2015, with rates higher in low- and middle-income countries [1]. Hypertension was responsible for around 47,000 deaths in South Africa in 2000. Since then, the prevalence of hypertension (SBP \geq 140 or DBP \geq 90 mmHg) has grown from around 25% to greater than 40% [2]."

Methods: Generally clear. There seemed to be no consideration of the likely time lags between the intervention, and the change in disease incidence.

Response – As our analysis is a static cost-of-illness and burden of disease study, we are not able to capture the benefits of interventions which seek to improve blood pressure control. We added text to our discussion which states:

"We estimated that expenditure on hypertension management represents a large proportion of the direct medical cost associated with the condition. It is likely that guideline-concordant care will lead to better controlled hypertension which will in turn reduce hypertension-related complications. Dynamic state transmission models can estimate the long-term health and cost consequences of interventions which seek to better control hypertension."

In the societal costs, it could be detailed that DALYs encompass premature deaths and years lived with disability in the productivity losses.

Response – Thank you for this suggestion. We have added a sentence in the *Complications – Event Rates* subsection of the *Methods* section titled which read:

"Disability-adjusted life years are a metric which combine both the years of life lost from a health-related condition alongside the years of healthy life lost due to disability [3]."

In addition, we updated the *Societal Costs* subsection of the *Methods* to state:

"A human capital approach was employed to calculate the societal cost of hypertension. This approach assumes that all healthy time lost due to illness (i.e.,

years of life lost and years of health life lost due to disability) leads to lost productivity [4].”

Also, regarding societal costs (productivity losses), the retirement age for men and women in South Africa is 60 years, so why were the estimates extended to 65 years of age?

Response – While the official pension age in South Africa is 60 years, it is common for individuals to work until the age of 65, as detailed in the Quarterly Labour Force Survey [5]. Your comment was helpful as it allowed us to re-assess data availability and the validity of our productivity estimates. We determined that we could more accurately predict the productivity losses associated with hypertension by combining data from the QLS 2020 and World Bank estimates of gross domestic product (GDP). Specifically, we assigned each DALY lost the value of “one GDP per worker” and weighted this value by the employment-to-population ratio. This method closely resembles the “productivity-adjusted life year” approach adopted by Hird et al. to estimate the cost of hypertension in Australia [6].

This Methodology is outlined in the *Societal Costs* subsection of the *Methods* section, which now reads:

“Every DALY experienced by an individual aged 20 to 65 years attributable to hypertension was assigned the value of one gross domestic product (GDP) per worker, weighted by the proportion of the overall population who are currently employed (the “employment-to-population ratio”) [6]. Societal costs were only included for the population without private health insurance. The GDP per worker for South Africa was estimated to be ZAR 276,000 (USD 19,500) [7,8]. The employment-to-population ratio was 43.3% for men and 33.2% for women [5].”

Sensitivity analysis is clear and explored well the influence of variables in the modeled results.

Response – Thank you.

Results: It would be helpful to detail the results based on sex differences.

Response – Thank you for this recommendation. In our original submission, we did not disaggregate model inputs or outputs by sex. We have now disaggregated model inputs and outputs. Specifically, we disaggregate population sizes, blood pressure category prevalence, rates of hypertension awareness, treatment, and control, rates of hypertension-related complications, and employment-to-population ratios.

When describing each input, we now highlight if it was disaggregated. This is shown in the quotations below. We have also included additional eTables which detail disaggregated inputs.

- Methods, Approach:
“Two worksheet-based costing models were developed in Microsoft Excel to synthesize data from multiple sources. One model was produced for men and another for women, due to previously observed sex differences in the age distribution of these populations, rates of hypertension and hypertension-related complications, and employment rates [2,5,9].”
- Methods, Population Size and Public Healthcare Utilization:
“Population size was informed by Statistics South Africa (SSA) mid-year estimates, disaggregated by sex [10].”
- Methods, Hypertension Rates:

“Hypertension prevalence, diagnosis, treatment, and control rates were estimated for the overall population and separately for men and women.”

- **Methods, Complications – Event Rates:**
“Overall rates of conditions which may be caused by hypertension were derived from the Global Burden of Disease Survey (GBDS) 2019, which combined multiple national surveys of demographics and health to produce sex-disaggregated estimates of incidence, prevalence, and disability-adjusted life years (DALYs) for different illnesses in South Africa [11].”
- **Methods, Societal Costs:**
“The employment-to-population ratio was 43.3% for men and 33.2% for women [5].”

When describing each result, we now describe disaggregated outcomes. This is shown in the quotations below. We have also included additional eTables which detail disaggregated outputs.

- **Results, Burden of Disease:**
*“Rates of both hypertension and medication use were greater for women and increased with age (**Table 3, eTable 9**).”*
- **Results, Burden of Disease:**
“Diagnosis of existent hypertension, likelihood of receiving treatment, and likelihood of BP control on treatment were substantially higher for women and increased with age.”
- **Results, Burden of Disease:**
*“Women were estimated to experience more hypertensive crises, hypertension-related strokes, hypertension related CKD events, and 50.6% of total hypertension-related DALYs (**eTable 13**).”*
- **Results, Burden of Disease:**
*“Direct medical costs of hypertension were higher for women (ZAR 6.11 billion or USD 0.431 billion) compared to men (ZAR 3.97 billion or USD 0.280 billion) (**eTable 14**). Conversely, societal costs of hypertension were lower for women (ZAR 10.5 billion or USD 0.743 billion) compared to men (ZAR 18.9 billion or USD 1.33 billion).”*

Table 4 should include 95% CI.

Thank you for this recommendation, these confidence intervals have now been added to **Table 4** and **eTable 14**. In addition, we added explanation to the *Approach* subsection of the *Methods* section to explain that model inputs that were stochastically sampled in probabilistic sensitivity analysis to derive distributions for costs and health outcomes:

“The costing models accept a range of epidemiologic and cost inputs, which are described below, and output rates of hypertension-related complications, direct medical costs, and societal costs associated with hypertension. Confidence intervals were derived for hypertension-related complications and costs through probabilistic analysis. We probabilistically sampled epidemiologic model input parameters and produced 1,000 estimates of hypertension-related health and cost outcomes. We reported mean and 95% confidence intervals for all model outputs.”

Discussion: The estimates are associated to the economic burden of hypertension to the public health system, so the overall costs of disease are even higher (considering the population covered by private

health care). The estimates rely on the GBD estimates, therefore the general limitations related to the GBD data should be added to the discussion.

Response – Thank you for these suggestions.

The Discussion section has been updated to read:

“While the majority of South Africans receive care in the public healthcare system, around 15% have private health insurance. We did not quantify the health and economic costs associated with hypertension in privately insured individuals. Previous studies have shown that income is not a significant predictor of elevated BP in South Africa but is a major determinant of hypertension awareness, treatment, and control [12,13]. Higher income individuals, including those with private health insurance, are more likely to receive treatment and are more likely to be employed. The average cost of hypertension management and the societal cost of hypertension-related complications may be greater in this population. Conversely, rates of hypertension-related complications are likely lower in this population due to better BP control.”

The Limitations section has been updated to read:

“We used the GBDS 2019 to estimate rates of hypertension-related complications. The GBDS is a wide-ranging study which estimates disease incidence, prevalence, and severity in 204 countries and territories. It accomplishes this by synthesizing local epidemiologic data using complex statistical models [14]. This multi-country approach to modelling in the GBDS survey may lead researchers to overlook important local insights. For example, Pillay-van Wyk et al. reformulated South African mortality data to correct for misclassified HIV/AIDS mortality [15]. They found that these adjustments led to significant variation between local and GBDS estimates of mortality and morbidity for several conditions including HHD and stroke. We reflected uncertainty in GBDS estimates by varying incidence, prevalence, and DALYs in one-way and probabilistic sensitivity analyses.”

Reviewer 2

Dr. Nicole Fraser-Hurt, The World Bank Group

Comments to the Author: This is a very important and well executed analysis. It employs a thorough approach to estimate health, cost and economic burdens in the uninsured South African population. Congratulations to the researchers. My comments and suggestions are all minor.

Response – Thank you for taking time to review our paper and thank you for your helpful comments and suggestions.

P6, line 52: “Individuals who met two criteria (e.g., SBP 150 mm Hg and DBP 105 mm Hg) were included in the more severe hypertension category.” You present the grade 3/severe category and then give this example of a case with grades 1b/2 BP data, calling it ‘more severe’. This is confusing.

Response – Apologies, this was poorly explained in the original submission. The text has been updated to read:

“If an individual had differential grades of systolic and diastolic BP, they were assigned the more severe of the two categories. For example, an individual with SBP 150 mm Hg (Grade 1) and DBP 105 mm Hg (Grade 2) would be assigned Grade 2 hypertension.”

P9, line 54: If hypertension was skewed toward poorer population groups then the 1 GDP/capita assumption may be an overestimate of the cost of lost productivity due to very low incomes? Given

the estimations have shown sensitivity to this assumption, you could add a caveat that you did not take into account the distribution of hypertension by income levels in the lost productivity estimates?

Response – Thank you, yes, we have averaged over potential heterogeneity that could occur if the distribution of hypertension is skewed across the population. We have added the following note to the *Discussion* section:

“While the majority of South Africans receive care in the public healthcare system, around 15% have private health insurance. We did not quantify the health and economic costs associated with hypertension in privately insured individuals. Previous studies have shown that income is not a significant predictor of elevated BP in South Africa but is a major determinant of hypertension awareness, treatment, and control [12,13]. Higher income individuals, including those with private health insurance, are more likely to receive treatment and are more likely to be employed. The average cost of hypertension management and the societal cost of hypertension-related complications may be greater in this population. Conversely, rates of hypertension-related complications are likely lower in this population due to better BP control.”

P11, line 27: You mention that hypertension prevalence had, among other factors, a large impact on total cost estimates, and that substantial reductions in direct medical and societal costs could be achieved if the prevalence of hypertension were to be reduced. Doesn't the poor treatment success among those diagnosed and on treatment also have a major effect on costs? Less than half of those diagnosed are controlling their BP (est. 46%), which compares well to many other countries but nevertheless drives the total costs.

Page 13, line 6: You conclude that “Research is required to establish priority cost-effective strategies for lowering rates of hypertension and preventing complications”. Isn't much of this research available, and now needs to be translated into quality service delivery, where guidelines are implemented and care is convenient and accessible? You could emphasize in the conclusions that improvements in the management of the already diagnosed hypertension cases is urgently needed to avert costs of illness to the health sector and society.

Response – We believe both comments above are valid and highlight the need for immediate roll-out of cost-effective interventions to improve outcomes for patients currently receiving hypertension treatment. We have amended the *Discussion* section to include the following paragraph:

“We estimated that expenditure on hypertension management represents a large proportion of the direct medical costs associated with the condition. It is likely that guideline-concordant care will lead to better controlled hypertension which will in turn reduce hypertension-related complications. Dynamic state transmission models can estimate the long-term health and cost consequences of interventions which seek to better control hypertension. Previous studies have shown that scaling up current hypertension treatment guidelines would be cost-effective for the healthcare sector [16]. Programmes which train community health workers about hypertension to improve medication adherence are also cost-effective [17]. Such interventions are urgently required to save healthcare costs and ultimately improve population health. Further research should establish additional cost-effective strategies to upscale and improve hypertension care.”

Table 1: Hypertension-related complications – Does this include costs of rehabilitation?

Response – As recommended in the Adult Primary Care guidelines, individuals experiencing a stroke received one visit with a physiotherapist and one visit with an occupational therapist. Additionally, we included costs for one physiotherapist visit post-transplant. In the *Complications – Costs* subsection of the *Methods* section we have updated the text to read:

“For acute events, we itemized costs for one hospitalization and subsequent rehabilitative services (i.e., physiotherapy and occupation therapy for stroke and transplant patients)

Correct the cost for physician visit (typo) - 17.11.00 Table 4: CKD complications – the costs in the two currencies don't match (ZAR 19 / USD 94)

Response – Thank you for highlighting this typographic mistake, we have corrected this number in the table (to 17.11).

Supplement: II. Treatment to Manage Hypertension – You clearly cost the implementation of this multi-step treatment escalation guidance. It might be useful to mention it in the text that you are guideline-costing and not actual treatment as implemented in practice.

Response – This is an important assumption in the paper. We elicited the opinion of experts to determine the likelihood that clinicians would adhere to the National Department of Health's Adult Primary Care Guidelines when making this assumption. We have updated the text in the *Management Costs* subsection of the *Methods* section to read:

“We were not able to estimate clinician compliance to APC guidelines. We assumed that all treated patients received guideline-compliant care and expert opinion was elicited to validate this assumption.”

In addition, when discussing the collection and dissemination of routine clinical data in the South African public healthcare system in the *Discussion* section, we have added the comment:

“...our study would have benefited from information on clinical compliance to APC guidelines for hypertension management.”

Supplemental Tables 4, 5 and 7: Please indicate which costs are annual

Response – These tables have been updated accordingly. Please note that this now refers to **eTables 5, 6, and 8**, due to the addition of extra tables to reflect sex differences in model inputs and outputs.

VERSION 2 – REVIEW

REVIEWER	Eduardo Augusto Fernandes Nilson Ministry of Health of Brazil, Department of Health Promotion
REVIEW RETURNED	25-Dec-2021
GENERAL COMMENTS	The suggestions by the peer reviewers were incorporated in the new version of the manuscript.